REMARKS

Claims 1-4, 8-11, 15-17, 21-24, 28-29, 31-36, 40-45 and 48-51 were pending in the application. Claims 1-4, 8-11, 28-29, 32, 33, 36, 50 and 51 have been canceled without prejudice. Claims 15, 21, 31 and 42 have been amended. New claims 52-53 have been added. Accordingly, upon entry of the amendments presented herein, claims 15-17, 21-24, 31, 34-35, 40-45, 48-49 and 52-53 will remain pending in the application.

No new matter has been added. Support for the amendments to the claims can be found in the claims and throughout the specification as originally filed.

Amendments to and cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and were done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Acknowledgement of the Withdrawal of Previous Rejections

Applicants gratefully acknowledge the withdrawal of: (a) the previous rejection of claims 1-4, 8-11, 15-17, 21-24, 28-29, 31 and 43 under 35 U.S.C. § 102(b) as being anticipated by Adair *et al.* (U.S. Patent No. 5,994,510); (b) the previous rejection of claims 1-4, 8-11, 15-17, 21-24, 28, 29, 31-36, 40-45 and 48-49 under the doctrine of obviousness-type double patenting as being unpatentable over claims 1-100 of Salfeld *et al.* (U.S. Patent No. 6,509,105) in view of Adair *et al.* and Salfeld *et al.* (U.S. Patent No. 6,258,562).

Rejection of Claims 1-4, 8-11, 15-17, 21-24, 28-29, 31-36, 40-45 and 48-51 Under 35 U.S.C. 112, Second Paragraph

The Examiner has rejected claims 1-4, 8-11, 15-17, 21-24, 28-29, 31-36, 40-45 and 48-49 under 35 U.S.C. 112, second paragraph as being indefinite for reciting of "an effective amount of a human anti-TNFα antibody...in a low dose of 0.01-0.1 mg/kg." Specifically, the Examiner is of the opinion that "the phrase..., given its broadest reasonable interpretation consistent with the instant specification[,] could be interpreted as reading on the administration

of almost ***any*** amount of anti- TNFα antibody..." and, therefore, that the metes and bounds of this phrase are not clear.

Claims 1-4, 8-11, 28, 29, 32, 33, 36, 50 and 51 have been canceled, thereby rendering the rejection moot as it pertains to these claims. With respect to the remaining claims, Applicants respectfully traverse the Examiner's rejection on the grounds that the claims are clear and definite. However, in the interest of expediting prosecution, and in no way acquiescing to the validity of the Examiner's rejection, claims 15 and 21, and claims 16-17, 22-24, 31, 34, 35, 40 and 41 which depend therefrom, have been amended to delete the phrase "an effective amount," thereby rendering the rejection moot as it pertains to these claims. With respect to claims 42 and 48, and claims 43-45 and 49 which depend therefrom, respectively, Applicants respectfully point out that these claims do not recite the phrase "an effective amount." These claims are directed to a low dose method for treating rheumatoid arthritis or improving symptoms in the joints of a subject having arthritis comprising "administering to a subject a low dose of 0.01-0.1 mg/kg of a human anti- TNFα antibody, or antigen-binding portion thereof." Accordingly, Applicants submit that the rejection of claims 42-45 and 48-49 as being indefinite is improper and respectfully request that the rejection be reconsidered and withdrawn.

Rejection of Claims 1, 8, 28, 29, 31-33, 35, 36 and 50-51
Under 35 U.S.C. 112, First Paragraph, Written Description

The Examiner has rejected claims 1, 8, 28, 29, 31-33, 35, 36 and 50-51 under 35 U.S.C. 112, first paragraph as allegedly failing to comply with the written description requirement. Specifically, the Examiner is of the opinion that "this disclosure describes a method of treating arthritis symptoms of a particular ***disease species*** in which TNFα activity is detrimental, rheumatoid arthritis, with the claimed dosages, ***BUT*** it does ***not*** reach a method of treating the ***genus of diseases*** in which TNFα is detrimental with the ***particular dosage*** of 0.01 mg/kg – 0.1 mg/kg." The Examiner concludes that the pending claims "broaden the scope of the instant disclosure as-filed and introduce new concepts, which violates the written description requirement of the first paragraph of 35 U.S.C. 112."

Applicants respectfully traverse the Examiner's rejection on the grounds that, based on the teachings in Applicants' specification and the general knowledge in the art, one of ordinary skill in the art would understand that Applicants were in possession of the claimed invention at

the time of filing the application. However, in the interest of expediting prosecution, and in no way acquiescing to the validity of the Examiner's rejection, claims 1, 8, 28, 29, 32-33, 36 and 50-51 have been canceled without prejudice, and claim 31 has been amended so that it depends on claims 15 or 21, thereby rendering this rejection moot as it pertains to these claims. With respect to claim 35, Applicants respectfully point out that this claim depends from claims 21-22, which are directed to methods for alleviating symptoms associated with arthritis. The Examiner has admitted that Applicants' specification describes a method of treating arthritis with the claimed dosages.

In view of all of the foregoing, Applicants submit that this rejection under 35 U.S.C. 112, first paragraph for lack of written description is improper and respectfully request that the rejection be reconsidered and withdrawn.

Rejection of Claims 1-4, 8-11, 15-17, 21-24, 28, 29, 31-36, 40-45 and 48-51 Under 35 U.S.C. 112, First Paragraph, Enablement

The Examiner has rejected claims 1-4, 8-11, 15-17, 21-24, 28, 29, 31-36, 40-45 and 48-51 under 35 U.S.C. 112, first paragraph as failing to comply with the enablement requirement. Specifically, the Examiner is of the opinion that "[n]either D2E7 nor Remicade appear to show any consistent effect on arthritic scores when dosed at 0.01 mg/kg once per week for 10 weeks (see, in particular, Example 1, part B and Figures 1, 2 and 4)." The Examiner further alleges that "as a second measure of treatment efficacy, four histophathological features were measured at the end of the 10 week treatment. Again, neither D2E7 nor Remicade appear to be able to elicit an improvement in the measured histological features at the 0.01 mg/kg dose (see, in particular, Example 1, part D and Figure 5)." The Examiner concludes that "undue experimentation would be required to practice the claimed invention commensurate with the scope of the claims from the written disclosure alone."

Claims 1-4, 8-11, 28, 29, 32, 33, 36, 50 and 51 have been canceled, thereby rendering this rejection moot as it pertains to these claims.

With respect to claims 15-17, 21-24, 31, 34-35, 40-45 and 48-49, Applicants respectfully traverse this rejection for the following reasons. Section 112 does not require that Applicants describe every equivalent within the scope of the claims so long as the specification provides sufficient teachings for a person of skill in the art to identify additional equivalents ***without***

undue experimentation (In re Wands 8 USPQ2d 1400-1407, 1404 (CAFC, 1988)). The fact that some experimentation is required does not preclude a finding of enablement. See, *e.g.*, In re Angstadt, 537 F.2d 498, 503 and Amgen Inc. v. Chugai Pharmaceutical Co., Ltd., 927 F.2d 1200, 1213 (CAFC 1991). Moreover, "as long as the specification discloses ***at least one method*** for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of §112 is satisfied." In re Fischer, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (emphasis added).

Applicants respectfully submit that based on the teachings in Applicants' specification as well as the general knowledge in the art, one of skill in the art would be able to make and use the claimed invention using only routine experimentation.

Contrary to the Examiner's assertion, Applicants provide data demonstrating the effectiveness of anti-TNFα antibodies, including D2E7 and Remicade, at the claimed dose range. For example, Figure 5 depicts the evaluation of the effects of anti-TNFα antibodies (including D2E7 and Remicade) administered to mice over a dose range of 0.01 mg/kg -10 mg/kg, including the doses of 0.01 mg/kg and 0.1 mg/kg, the lower and upper limit, respectively, of the claimed dosage range, on relieving symptoms commonly associated with arthritis (*e.g.*, inflammation, vascularity, cartilage erosion and bone erosion). Treatment of arthritis symptoms is evidenced by an analysis of microscopic signs of disease activity in the arthritic joints of the mice. As shown in Figure 5, at the lower range of the claimed dose range, *i.e.*, 0.01 mg/kg, both D2E7 and Remicade showed a positive effect on cartilage erosion, while Remicade showed a positive effect on bone erosion. At the higher range of the claimed dose range, *i.e.*, 0.1 mg/kg, D2E7 produced a marked effect on each of inflammation, cartilage erosion, vascularity and bone erosion, while Remicade showed a positive effect on vascularity.

Further, Table 2 at page 29 of the specification discloses the approximate ED_{50} (the amount of anti-TNFα inhibitor required ***to affect 50% of the animals***) determined for the treatment of the arthritic symptoms by the anti-TNFα inhibitors. Although D2E7 and Remicade exhibited slightly varied responses, these antibodies were both effective in reducing inflammation, vascularity, cartilage erosion and bone erosion within the claimed range. For example, Remicade was effective in reducing vascularity, cartilage erosion and bone erosion at a dose falling within the claimed range (see Table 2 at page 29 of the specification). D2E7 was also effective in reducing inflammation, vascularity, cartilage erosion and bone erosion at a dose falling within the claimed range (see Table 2 at page 29 of the specification). In particular, the

approximate ED_{50} for D2E7 is ***0.1 mg/kg*** for the treatment of inflammation and vascularity and ***between 0.01 and 0.1 mg/kg*** for the treatment of cartilage and bone erosion. The approximate ED_{50} for Remicade is ***0.1 mg/kg*** for the treatment of vascularity and between ***0.1*** and 0.5 mg/kg for the treatment of cartilage erosion and bone erosion. Given that the ED_{50} represents the amount of TNFα antibody required ***to affect 50% of the animals***, one of ordinary skill in the art would recognize that a range of doses surrounding the ED_{50} dose would also have a therapeutic effect on a portion of the patient population. Thus, the examples provided in the specification demonstrate that the claimed low dose methods may be successfully practiced using at least two different TNFα antibodies.

Moreover, the specification provides sufficient teachings such that a person of skill in the art would be able to identify specific doses of an anti-TNFα antibody within the claimed dose range suitable for use in the claimed methods without undue experimentation. For example, the specification describes in Example 1, at pages 26-30, experiments which can be carried out in a mouse model to evaluate the efficacy of a particular TNFα antibody in alleviating arthritic symptoms over the claimed dosage range. In particular, Example 1b teaches evaluation of development of arthritis and Example 1(d) teaches microscopic analysis of vascularity, inflammation, cartilage, and bone erosion to evaluate the efficacy of a TNFα inhibitor. One of skill in the art would recognize that these assays taught in the specification may be used to evaluate and identify specific doses of TNFα antibodies within the claimed dose range useful in the claimed methods. Thus, given the extensive guidelines and working examples provided by Applicants, combined with the high skill level in the art, testing of a given TNFα antibody at a particular low dose within the claimed dose range of 0.01-0.1 mg/kg for use in the subject invention would not constitute undue experimentation.

In summary, Applicants respectfully submit that, in view of the ample teachings provided in the specification and the extensive knowledge available in the art, a person of ordinary skill in the art would be able to make and use the claimed methods using only routine experimentation. Accordingly, Applicants respectfully request that the rejection of claims 1-4, 8-11, 15-17, 21-24, 28, 29, 31-36, 40-45 and 48-51 under 35 U.S.C. 112, first paragraph, for lack of enablement be reconsidered and withdrawn.

Rejection of Claims 1-4, 8-11, 15-17, 21-24, 28-29, 31-36, 40-45 and 48-51 Under 35 U.S.C. § 102(b)

The Examiner has maintained the rejection of claims 1-4, 8-11, 15-17, 21-24, 28-29, 31-36, 40-45 and 48-49, and has additionally rejected claims 50-51, under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 6,258,562 in the name of Salfeld *et al.* (hereinafter referred to as "the '562 patent"). In particular, the Examiner is of the opinion that "the instantly claimed invention is taught by Salfeld *et al.* with 'sufficient specificity to constitute an anticipation under the statute.'" The Examiner alleges that

> [t]he instant situation is analogous to that of Ex parte Lee, 31 USPQ2d 1105, where a claim for a thermoplastic composition having a melt index of ***less than about 5*** was found to be anticipated by prior reference disclosing identical compositions having a ***broader melt index range of 0.1 to 40***. In an en banc 5-2 ruling the U.S. Board of Patent Appeals and Interferences decided that the disclosure of the range **0.1** to 40 **constitutes a specific disclosure of discrete embodiment of claimed invention**, i.e., 0.1, and thus the prior art anticipated the claimed invention.
>
> 'It has long been held that the disclosure in the prior art of any value within a claimed range is an anticipation of the claimed range. See, merely for example, In re Wertheim, 541 F.2d 257, 267, 191 USPQ 90, 100 (CCPA 1976). We discern no reason for treating the specific value disclosed in the reference as the **lower limit of a range any differently from any other single value disclosed in a reference**. Thus, on the record before us, we conclude that the reference, at least on its face, anticipates the invention claimed here.' See Ex parte Lee, *ibid* (emphasis added).

Claims 1-4, 8-11, 28, 29, 32, 33, 36, 50 and 51 have been canceled without prejudice, thereby rendering this rejection moot as it pertains to these claims.

With respect to claims 15-17, 21-24, 31, 34-35, 40-45 and 48-49, Applicants respectfully traverse this rejection for the following reasons. Contrary to the Examiner's assertion, the en banc 5-2 ruling of the U.S. Board of Patent Appeals and Interferences, which held that the claimed range was anticipated by the range disclosed in the prior art reference, did not agree that "the disclosure of the range **0.1** to 40 constitutes a specific disclosure of discrete embodiment of claimed invention, *i.e.*, 0.1," and thereby anticipates the claimed invention. The statement

quoted by the Examiner from Ex parte Lee of "[w]e discern no reason for treating the specific value disclosed in the reference as the ***lower limit of a range any differently from any other single value disclosed in a reference,"*** represents the opinion of three members of the plurality opinion. The Examiner fails to point out the footnote to this statement in Ex parte Lee, which clarifies that "an expanded panel was convened in this case because it came to light that the Examiners-in-chief were not unanimous on this issue and that, as a result, inconsistent decisions could be reached by different panels." Indeed, Examiners-in Chief W. Smith and McCandlish disagree with this reasoning in their concurring opinion. Specifically, these Examiners indicate that

> [w]hile not clearly delineated by the plurality, ***the reason this panel was expanded was to determine whether the end points of ranges disclosed in a reference should be treated as discrete species or working examples***... The determination of what specific compositions are described in a reference where a property of a component of the composition is disclosed in terms of a range of values, as here, must be made on a case by case basis. The ***endpoints of a range may have greater or lesser significance depending on the total disclosure of the reference. The attempt of the plurality to arrive at a hard and fast rule on the significance of an end point value of a range, in order to determine whether a reference is anticipatory or only constitutes evidence of obviousness, is futile. Such a rule is bound to be defined more by its exceptions. Rather, our efforts should be directed to emphasizing that issues such as these must be considered on a case by case basis***. As stated by the court in In re Ruscetta, 255 F.2d 687, 118 USPQ 101 (CCPA 1958):
>
> [We] deem it advisable to ***reiterate the warnings given in the past*** by Judge Hatfield in *Conover v. Downs, 17 C.C. P.A. (Patents) 587, 592, 35 F.2d 59, 3 USPQ 58, 60*, and Judge O'Connell in *In re Newton, 38 C.C. P.A. (Patents) 877, 880, 187 F.2d 337, 88 USPQ 554, 556*, that ***undue liberties should not be taken with court decisions***, which should be construed in accordance with the precise issue before the court, and that a ***fertile source of error*** in patent law is the ***misapplication of a sound legal principle established in one case to another case in which the facts are essentially different*** and the principle has no application whatsoever (emphasis added). Ex parte Lee, *ibid.*

Further, Applicants wish to point out that Examiners-in-Chief Pellman and Steiner, in a dissenting opinion, similarly to the concurring opinion, disagree with the reasoning of the plurality opinion. The dissenting opinion states:

> [t]he appealed claims define a class of compositions which overlap to a small extent those disclosed by Lee... That some of the claimed compositions are buried within Lee's broad disclosure and brought to light by appellant, does not mean that Lee describes the claimed invention within the meaning of 35 U.S.C. 102.
>
> Unable to point to any disclosed anticipating composition, ***the plurality holds, as a matter of law, that the endpoint of a disclosed range for a parameter constitutes a description of a patentability-defeating species under 35 U.S.C. 102*** of a composition comprising two polymers, one of which exhibits said endpoint parameter. ***This is pure fiction.***
>
> In our opinion, the plurality view is without precedential support. ***We do not share the plurality's fatal attraction to the endpoint of a disclosed range. The apparent visibility of an endpoint is not a license to create a patentability-defeating species under 35 U.S.C. 102*** thereby depriving appellant of the opportunity to demonstrate that the selection of a polyolefin additive having a very restricted range of melt indexes unexpectedly solves the delamination problem.

Thus, in summary, Applicants submit that the Examiner is relying upon the reasoning of the minority, *i.*e., three of the seven members of the U.S. Board of Patent Appeals and Interferences, which decided Ex parte Lee. The reasoning of the majority, *i.e.*, the concurring opinion and the dissenting opinion, ***does not agree*** that the end point of a range ***necessarily*** constitutes a disclosure of a discrete embodiment of an invention that is anticipatory of a range encompassing it, but rather emphasizes that such issues ***must be considered on a case by case basis***.

Applicants respectfully submit that, contrary to the Examiner's assertion, the instant situation is not analogous to that of Ex parte Lee. Indeed, the facts of the instant case are different from those of Ex parte Lee and should be considered independently. In particular, in Ex parte Lee, the claimed range for a melt index of "less than about 5" ***substantially overlaps*** with the range disclosed in the prior art reference of "0.1 to 40" (*i.e.*, overlaps between 0.1 and 5, which is ***almost the whole claimed range***). In contrast, in the present case, the claimed range of 0.01-0.1 mg/kg only "***touches***" the range of 0.1-20 mg/kg disclosed by the '562 patent.

The concurring opinion states that

> [t]he plurality ***focuses only on the composition of Lee where the LLDPE resin component has a melt index of 0.1 since that is the lower end point value and***

> ***does not set forth whether the other compositions disclosed by Lee containing a LLDPE resin component having a melt index value within the claimed range are also anticipatory***. Without clarifying whether these other compositions are also described with sufficient specificity so as to support a finding of anticipation, ***the plurality, in effect, elevates the composition of Lee where the LLDPE resin component has a melt index value of 0.1 to a status beyond any other composition described by Lee which is encompassed by the claims on appeal.*** We see no basis on this record for such disparate treatment. Ex parte Lee, *ibid.*

The concurring opinion notes that "among the multitude of compositions disclosed by Lee are those which comprise a polyphenylene ether resin and LLDPE resin having a melt index of >/=0.1...to 'less than 5'... and conclude that "these compositions are described with sufficient specificity by Lee" to anticipate the claimed invention. As discussed above, unlike the situation in Ex parte Lee, where a "multitude of compositions" disclosed by the prior reference comprise a melt index falling within the claimed range, in the instant case, the lower end point value of a dose range disclosed by the reference (0.01 mg/kg) merely "touches" the claimed range (0.01-0.1 mg/kg). Thus, unlike in Ex parte Lee, where the prior reference was found to anticipate the claimed invention, here, the '562 patent fails to teach or suggest the claimed narrow range of 0.01-0.1 mg/kg with ***sufficient specificity*** to constitute an anticipation of the pending claims.

Moreover, Applicants reiterate the arguments set forth in the prior Response filed November 17, 2006. As discussed in the Response filed November 17, 2006, the MPEP § 2131.03 specifically provides guidelines for determining whether a particular ***range*** taught in the prior art anticipates a claimed ***range***, where the prior art range either ***touches, overlaps*** or ***falls within*** the claimed range:

> "If the claims are directed to a ***narrow range,*** the [prior art] reference teaches a ***broad range,*** and there is ***evidence of unexpected results within the claimed narrow range,*** depending on the other facts of the case, ***it may be reasonable to conclude that the narrow range is not disclosed with 'sufficient specificity' to constitute an anticipation of the claims.***" (See M.P.E.P. § 2131.03; *emphasis added*).

In the instant case, the '015 patent discloses a dose range (0.1-20 mg/kg) which ***touches*** the claimed range (0.01-0.1 mg/kg), but fails to disclose a ***specific example*** falling within the claimed range. Further, the pending claims are directed to a ***narrow*** range of 0.01-0.1 mg/kg, while the '015 patent discloses a much ***broader*** range of 0.1-20 mg/kg. Finally, the instant specification discloses the ***unexpected discovery*** that the claimed low dose of 0.01-0.1 mg/kg of

a TNFα antibody can be effective in treating arthritis and alleviating symptoms associated with arthritis. Thus, the '015 patent fails to teach or suggest the claimed narrow range of 0.01-0.1mg/kg with sufficient specificity to constitute an anticipation of the claims.

In view of the foregoing, it is evident that the '562 patent fails to teach or suggest the claimed narrow range of 0.01-0.1 mg/kg with ***sufficient specificity*** to constitute an anticipation of the pending claims. Accordingly, Applicants respectfully request that the rejection of claims 1-4, 8-11, 15-17, 21-24, 28-29, 31-36, 40-45 and 48-51 under 35 U.S.C. 102(b) as lacking novelty over the '562 patent be reconsidered and withdrawn.

Rejection of Claims 1-4, 8-11, 15-17, 21-24, 28-29, 31-36, 40-45 and 48-51 Under 35 U.S.C. § 102(e)

The Examiner has maintained the rejection of claims 1-4, 8-11, 15-17, 21-24, 28-29, 31-36, 40-45 and 48-49, and has additionally rejected claims 50-51, under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,509,015 in the name of Salfeld *et al.* (hereinafter referred to as "the '015 patent") for the same reasons as discussed above with respect to the '562 patent.

Claims 1-4, 8-11, 28, 29, 32, 33, 36, 50 and 51 have been canceled, thereby rendering this rejection moot as it pertains to these claims.

With respect to claims 15-17, 21-24, 31, 34-35, 40-45 and 48-49, Applicants respectfully traverse this rejection and maintain that the '015 patent fails to teach or suggest each and every element of the claimed invention in accordance with 35 U.S.C. §102(e). The '015 patent fails to anticipate the claimed invention in that there is no teaching or suggestion in the '015 patent to use a low dose range ***of 0.01-0.1 mg/kg*** of a TNFα antibody. Indeed, there is no teaching or suggestion in the '015 patent to consider any doses which appear less efficacious in standard assays than saturating doses. As discussed above with respect to the '562 patent, when the prior art discloses a range which ***touches*** the claimed range, but ***no specific examples*** falling within the claimed range are disclosed, ***a case by case determination must be made as to anticipation.*** Applicants submit that the '015 patent fails to anticipate the claimed invention for the same reasons detailed above with respect to the '562 patent. Similar to the '562 patent, the facts of the '015 patent are different from those of Ex parte Lee. In particular, unlike the situation in Ex parte Lee, where a "multitude of compositions" disclosed by the prior reference comprise a melt

index falling within the claimed range, in the instant case, the lower end point value of a dose range disclosed by the reference (0.01 mg/kg) merely "touches" the claimed range (0.01-0.1 mg/kg). Thus, unlike in Ex parte Lee, where the prior reference was found to anticipate the claimed invention, here, the '015 patent fails to teach or suggest the claimed narrow range of 0.01-0.1 mg/kg with ***sufficient specificity*** to constitute an anticipation of the pending claims.

In view of the foregoing, Applicants submit that this rejection of claims 1-4, 8-11, 15-17, 21-24, 28-29, 31-36, 40-45 and 48-51 under §102(e) over the '015 patent is improper and respectfully request that it be reconsidered and withdrawn.

Rejection of Claims 15-24 Under 35 U.S.C. § 102(b)

The Examiner has rejected claims 15-24 under 35 U.S.C. § 102(b) as being anticipated by Stephens *et al.* (Antibody Therapeutic (1997), pp 317-340, eds. Harris *et al.*, CRC: Boca Raton, Fla.). The Examiner relies on Stephens *et al.* for teaching "a method of treating rheumatoid arthritis comprising administering a single 0.1 mg/kg dose of humanized anti-TNFα antibody, CDP571"; that "the disease activity measures included tender and swollen joints and that patients who received placebo did not improve whereas CDF571 had a dose-dependent effect on all patients treated"; and that "all patients receiving CDP571 scored a reduction in pain scale by week 1 (see entire document, in particular pages 326-327)." Based on the foregoing, the Examiner concludes that Stephens *et al.* anticipates the pending claims.

As an initial matter, Applicants respectfully point out that claims 18-20 were not pending as of the date of issuance of the present Office Action. Accordingly, Applicants will address this rejection only as it pertains to claims 15-17 and 21-24.

With respect to the claims 15-17 and 21-24, Applicants respectfully traverse this rejection on the grounds that Stephens *et al.* fails to teach or suggest each and every element of the claimed invention in accordance with 35 U.S.C. §102(b). For a prior art reference to anticipate a claimed invention under 35 U.S.C. 102, the prior art must teach *each and every element* of the claimed invention. *Lewmar Marine v. Barient*, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987).

Claim 15, and claims 16-17, which depend therefrom, are directed to a method for ***treating arthritis*** by administering to a subject an anti-TNFα antibody, or antigen-binding portion thereof, in a ***low dose of 0.01 – 0.1 mg/kg, such that the arthritis is treated.*** Claim 21,

and claims 22-24, which depend therefrom, are directed to a method for ***alleviating symptoms associated with arthritis*** by administering to a subject an anti-TNFα antibody, or antigen-binding portion thereof, in a ***low dose of 0.01 – 0.1 mg/kg, such that the symptoms are alleviated***.

Stephens *et al.* report on a clinical study in which patients with active rheumatoid arthritis received up to four rounds of administration of the humanized anti-TNFα antibody, CDP571. In the ***first round infusion***, patients received a single dose of ***0.1, 1 or 10 mg/kg*** over a period of 1 hour, and assessments of disease activity were conducted at 1, 2, 4 and 8 weeks after the infusion. Patients who experienced no adverse effects after the first infusion went on to receive ***second, third and fourth infusions*** at a dose of either ***1 or 10 mg/kg*** CDP471. Assessments of disease activity were conducted for 8 weeks, as above, solely after the second infusion. Stephens *et al.* report the results of the clinical study following the first round infusion in Tables 2 and 3 at page 328 and at pages 327-329. Notably, Stephens *et al.* provide ***no data*** for the group of patients who received 0.1 mg/kg in either Table 2 or Table 3 and, moreover, ***nowhere in the reference is it disclosed*** (*e.g.*, see, in particular, pages 327-329) ***that the dose of 0.1 mg/kg CDP571 had any effect in treating arthritis***. Indeed, Stephens *et al.* provide data and report effective treatment of arthritis ***only for the group of patients who received doses of 1 or 10 mg/kg*** in the first round infusion. Moreover, as noted by the Examiner, Stephens *et al.* report that

> [f]ollowing repeated doses, the immune response and pharmacokinetic profiles suggest that ***at higher doses a state of high dose tolerance is reached, anti-CDP571 antibodies are no longer detectable***, and the clearance rate is prolonged.... ***A single dose at 10 mg/kg may be sufficient to induce tolerance*** and subsequent lower doses maintain this state... The class of anti-CD571... produced in these patients is IgM and little or no switch to IgG was detected. ***In contrast, patients receiving 0.1 mg/kg*** (and one patient receiving 10 mg/kg) ***tended to show a class-switch to IgG anti-CDP571 production by 8 weeks following their first dose*** and subsequent doses of CDP471, whether at 1 or 10 mg/kg, boosted specific IgG production, ***resulting in increased clearance of CDP571***. (Emphasis added).

Thus, Stephens *et al.* disclose that a 0.1 mg/kg dose of CDP571 results in enhanced production of anti-CDP571 antibodies and, as a consequence, ***increased clearance of CDP571*** from the patient's system, as compared to a higher dose, *e.g.*, 1 or 10 mg/kg. In view of the foregoing, it is evident that Stephens *et al.* fail to teach or suggest a method of ***treating arthritis*** or ***alleviating symptoms associated with arthritis*** by administering to a subject an anti-TNFα antibody, or

antigen-binding portion thereof, in a low dose of ***0.01 – 0.1 mg/kg***, such that the ***arthritis is treated or symptoms are alleviated.***

Moreover, even if the Examiner were to raise a rejection based on inherent anticipation in view of Stephens *et al.*, Applicants respectfully submit that Stephens *et al.* expressly teach that the lower dose of 0.1 mg/kg is not effective in treating arthritis, e.g., rheumatoid arthritis, or symptoms associated with arthritis. As pointed out above, Stephens *et al.* teach that at the 0.1 mg/kg dose the administered antibody is rapidly cleared. As also highlighted above, Stephens *et al.* report that the 0.1 mg/kg dose was not effective in treating arthritis (see notable absence of any results for this dose from Tables 2 and 3). Finally, the fact that in the second, third and fourth infusions the 0.1 mg/kg dose was not even used clearly indicates that, indeed, this dose was not effective in treating arthritis, *e.g.*, rheumatoid arthritis, or symptoms associated with arthritis.

In summary, it is evident that Stephens *et al.* fails to teach each and every element of the claims, and therefore, fails to anticipate the claimed invention. Accordingly, Applicants respectfully request that the rejection of claims 15-24 under 35 U.S.C. § 102(b) over Stephens *et al.* be reconsidered and withdrawn.

Rejection of Claims 1-4, 8-11, 15-17, 21-24, 28, 29, 31-36, 40-45 and 48-51 Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1-4, 8-11, 15-17, 21-24, 28, 29, 31-36, 40-45 and 48-51 under 35 U.S.C. § 103(a) as being obvious over Stephens *et al.* (Antibody Therapeutic (1997), pp 317-340, eds. Harris *et al.*, CRC: Boca Raton, Fla.) in view of Salfeld et al. (U.S. Patent No. 6,258,562; hereinafter referred to as "the '562 patent") and den Broeder *et al.* (Rheumatology 2002, 41(6):638-42). The Examiner relies on Stephens *et al.* for the reasons discussed above. The Examiner acknowledges that "the instant claims differ from Stephens in that they recite administration of a ***human*** anti-TNFα antibody, such as ***D2E7***."

The Examiner further relies on the '562 patent for teaching "a method of treating rheumatoid arthritis by administering a human anti-TNFα antibody, such as D2E7" and that "an effective dose of anti-TNFα antibody is 0.1-20 mg/kg." The Examiner further relies on den Broeder *et al.* for teaching "a clinical study performed with the fully human D2E7 anti-TNFα

antibody where rheumatoid arthritis patients were effectively treated with a 0.25 mg/kg/2-4 weeks," and for teaching that "by using the lowest possible dose of anti-TNFα antibody one can minimize the risk associated with TNFα suppression." The Examiner concludes that "it would have been obvious to one of ordinary skill in the art to substitute the D2E7 human anti-TNFα antibody of Salfeld for the CDP571 humanized anti-TNFα antibody of Stephens to treat rheumatoid arthritis patients at a dose of 0.1 mg/kg anti-TNFα antibody" and "given the teachings of den Broeder, one of ordinary skill in the art would have been motivated to treat rheumatoid arthritis with *the lowest possible effective dose* of anti-TNFα antibody, in order to minimize the risk associated with TNFα suppression."

Claims 1-4, 8-11, 28, 29, 32, 33, 36, 50 and 51 have been canceled, thereby rendering this rejection moot as it pertains to these claims. With respect to claims 15-17, 21-24, 31, 34-35, 40-45 and 48-49, Applicants respectfully traverse this rejection on the grounds that the claimed low dose methods would not have been obvious to one of ordinary skill in the art based on the teachings of Stephens *et al.*, the '562 patent and/or den Broeder *et al.*, alone and/or in combination.

To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been ***motivated*** to make the claimed invention and would have had a reasonable ***expectation of success*** in making the claimed invention. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). Moreover, when considering prior art disclosing a range which "touches" the claimed range, "unexpected results [within the claimed narrow range] may... render the claims unobvious" (see M.P.E.P. § 2131.03).

The claimed methods are unique in that they embody Applicants' unexpected discovery that a low dose of 0.01-0.1 mg/kg of a TNFα antibody can be effective in treating arthritis and alleviating symptoms associated with arthritis. Applicants teach in the specification various benefits associated with administering low doses of TNFα antibodies, including improvement in cartilage erosion (see, for example, Table 2 at page 29 of the specification). Applicants also

teach in the specification that low doses of a TNFα antibody may be advantageous as they may decrease side effects and may decrease the frequency of administration associated with the normally prescribed dose (see, for example, page 7, lines 20-22 of the specification).

In contrast, as discussed above with respect to the rejection of claims 15-24 under 35 U.S.C. 102(b), Stephens *et al.* fail to teach or suggest the treatment of arthritis at any dose within the dose range of 0.01-0.1 mg/kg as required by the present claims. As discussed above, Stephens *et al.* basically report that the dose of 0.1 mg/kg was not effective in treating arthritis, *e.g.*, rheumatoid arthritis, or symptoms associated with arthritis. Indeed, as noted by the Examiner, Stephens *et al.* disclose that a 0.1 mg/kg dose of CDP571 results in enhanced production of anti-CDP571 antibodies and, as a consequence, ***increased clearance of CDP571*** from the patient's system, as compared to a higher dose, *e.g.*, 10 mg/kg. Thus, Stephens *et al.* ***teach away*** from the claimed invention of treating arthritis by administering a low dose of 0.01-0.1 mg/kg of an anti-TNFα antibody. Specifically, one of ordinary skill in the art would not have been motivated, based on the disclosure of Stephens *et al.*, to treat arthritis with a low dose of 0.01-0.1 mg/kg, since Stephens *et al.* essentially teach that a 0.1 mg/kg dose of CDP571 is not effective in treating arthritis and, moreover, teach that a low dose of the antibody mounts an immune response and is cleared from the patient's system to a greater extent than a higher dose, *e.g.*, 10 mg/kg, of CDP571.

The '562 patent fails to make up for this deficiency. The '562 patent provides general guidance with regard to normally prescribed dosing. The '562 patent fails to teach or suggest methods which use a low dose of 0.01-0.1 mg/kg of a TNFα inhibitor. In particular, as acknowledged by the Examiner, the '562 patent teaches that a therapeutically effective dose range for human anti-TNFα antibodies is 0.1-20 mg/kg. Thus, the '562 patent fails to teach or suggest methods which use a ***low dose of 0.01-0.1 mg/kg of an anti-TNFα antibody or antigen-binding portion thereof***. Moreover, one of ordinary skill in the art would not have been motivated to arrive at the claimed invention, *i.e.*, to select the claimed dosage range of 0.01 to 0.1 mg/kg, based on the disclosure of the '562 patent, because the '562 patent already teaches the successful inhibition of human TNFα activity using a dosage range of 0.1-20 mg/kg. Further, ***when considering prior art disclosing a range which "touches" the claimed range, "unexpected results [within the claimed narrow range] may... render the claims unobvious"*** (see M.P.E.P. §2131.03). In the present case, while the '562 patent discloses a dose range which

"touches" the claimed dose range of 0.01-0.1 mg/kg, the unexpected results provided by Applicants further prove that the pending claims are unobvious over the teachings of the '562 patent.

Den Broeder *et al.*, like the '562 patent, fails to make up for the deficiencies of Stephens *et al.* Den Broeder *et al.* report on a clinical, dose titration study involving a cohort of patients that had ongoing, successful treatment of rheumatoid arthritis with D2E7 for at least a year prior to the dose titration study at a fixed dose of 3.0 mg/kg, and at an interval of every 2 or 4 weeks. These patients were subjected to a step-wise reduction in dose at regular dosing intervals (every 2 or 4 weeks), *e.g.*, from 3.0 to 1.0, 0.5 and eventually to 0.25 mg/kg. As part of the study design, "if a flair of the disease occurred, the dose of anti-TNFα was increased one step to the previous dose" (page 639, second column, second paragraph). Den Broeder *et al.* report the results of this study, wherein "six out of 21 patients were placed back on the original dose of 3.0 mg/kg after flaring on 1.0 mg/kg, whereas nine, three and three patients respectively reached a dose of 1.0, 0.5 and 0.25 mg/kg." Further, Den Broeder *et al.* disclose that, based on these results, "the ***median of the calculated weekly dose*** of anti-TNFα administered to these patients was ... 32.5 mg week" (page 641, second paragraph), which is equivalent to ***0.36 mg/kg*** per week for a 90 kg person. Thus, den Broeder *et al.* fail to teach or suggest a method of treating arthritis by administering a dose lower than 0.25 mg/kg, let alone a low dose of 0.01-0.1 mg/kg of a TNFα antibody, as required by the instant claims.

Moreover, one of skill in the art would not have been motivated, based on the disclosure of den Broeder *et al.*, to practice the claimed invention of treating arthritis at a low dose of 0.01-0.1 mg/kg. Notably, Den Broeder *et al.* teach that "[a] ***drawback*** of step-down dose titration is the ***inevitable disease flare*** in the titration phase" and note that "***eighteen out of 21 patients*** experienced a flair of the disease" (page 641, last paragraph; emphasis added). Indeed, ***only three out of 21 patients reached the dose of 0.25 mg/kg***, while the remaining ***18 patients experienced a flair in disease at even higher doses***. Thus, den Broeder *et al.* ***teaches away*** from the claimed low dose of 0.01-0.1 mg/kg in that it teaches that even at a dose of 0.25 mg/kg (or greater), 18 out of the 21 patients treated experienced a flair in disease. One of ordinary skill in the art would not have been motivated nor have had a reasonable expectation of success, based on the disclosure of den Broeder *et al.*, to treat with doses lower than 0.25 mg/kg, since only a small percentage of patients (i.e., 3 out of 21) were observed to reach the dose of ***0.25 mg/kg*** before exhibiting a flare in disease.

In view of all of the foregoing, it is evident that Stephens *et al.* in view of the teachings of the '562 patent and den Broeder *et al.* fail to render the claimed invention obvious. Accordingly, Applicants respectfully request that the rejection of claims 1-4, 8-11, 15-17, 21-24, 28, 29, 31-36, 40-45 and 48-51 under 35 U.S.C. 103(a) be reconsidered and withdrawn.

Rejection of Claims 1-4, 8-11, 15-17, 21-24, 28, 29, 31-36, 40-45 and 48-51 Under the Doctrine of Obviousness-Type Double Patenting

The Examiner has rejected claims 1-4, 8-11, 15-17, 21-24, 28, 29, 31-36, 40-45 and 48-51 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-100 of U.S. Patent No. 6,509,015 (the '015 patent) in view of the '562 patent and den Broeder *et al.*

The Examiner relies on the claims of the '015 patent as being "directed to a method of treating rheumatoid arthritis by administering an anti-TNFα antibody, alone or in combination with additional therapeutic agents." The Examiner acknowledges that the presently pending claims differ from the "reference teachings" in the recitation of a "dose of 0.01-0.1 mg/kg." The Examiner further relies on the '562 patent as teaching that "an effective dose of anti-TNFα antibody is 0.1-20 mg/kg." The Examiner further relies on den Broeder *et al.* for teaching "a clinical study performed with the fully human D2E7 anti-TNFα antibody where rheumatoid arthritis patients were effectively treated with a 0.25 mg/kg/2-4 weeks," and for teaching that "by using the lowest possible dose of anti-TNFα antibody one can minimize the risk associated with TNFα suppression." The Examiner alleges that "[g]iven the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention," and concludes, therefore, that "the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made."

Applicants respectfully traverse the aforementioned obviousness-type double patenting rejection on the grounds that the claimed low dose methods would not have been obvious to one of ordinary skill in the art based on the claims of the '015 patent in view of the teachings of the '562 patent and den Broeder *et al.*, alone and/or in combination.

A nonstatutory basis exists for a double patenting rejection when the claimed invention is an obvious variation of an invention in an issued patent (M.P.E.P. § 804(B)(1)). Accordingly, any analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. § 103 obviousness determination. *In re Braat*, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been ***motivated*** to make the claimed invention and would have had a reasonable ***expectation of success*** in making the claimed invention. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). Moreover, when considering prior art disclosing a range which "touches" the claimed range, "unexpected results [within the claimed narrow range] may... render the claims unobvious" (see M.P.E.P. § 2131.03).

The claimed methods are unique in that they embody Applicants' unexpected discovery that low doses, *e.g.*, 0.01-0.1 mg/kg, of TNFα antibodies can be effective in treating arthritis and alleviating symptoms associated with arthritis. Applicants teach in the specification various benefits associated with administering low doses of the TNFα antibodies, including improvement in cartilage erosion (see, for example, Table 2 at page 29 of the specification). Applicants also teach in the specification that low doses of a TNFα antibody may be advantageous as they may decrease side effects and may decrease the frequency of administration associated with the normally prescribed dose (see, for example, page 7, lines 20-22 of the specification). In contrast, the claims of the '015 patent are directed to methods for treating rheumatoid arthritis by administering a human anti-TNFα antibody. As acknowledged by the Examiner, the claims of the '015 patent ***fail to teach or suggest a low dose of 0.01 – 0.1 mg/kg*** of a human anti-TNFα antibody.

The '562 patent fails to make up for this deficiency. The '562 patent provides general guidance with regard to normally prescribed dosing. The '562 patent fails to teach or suggest methods which use a low dose of 0.01-0.1 mg/kg of a TNFα inhibitor. In particular, as

acknowledged by the Examiner, the '562 patent teaches that a therapeutically effective dose range for human anti-TNFα antibodies is 0.1-20 mg/kg. Thus, the '562 patent, similar to the claims of the '015 patent, fails to teach or suggest methods which use a ***low dose of 0.01-0.1 mg/kg of an anti-TNFα antibody or antigen-binding portion thereof***. Moreover, one of ordinary skill in the art would not have been motivated to arrive at the claimed invention, *i.e.*, to select the claimed dosage range of 0.01 to 0.1 mg/kg, based on the disclosure of the '562 patent, because the '562 patent already teaches the successful inhibition of human TNFα activity using a dosage range of 0.1-20 mg/kg. Further, as indicated above, ***when considering prior art disclosing a range which "touches" the claimed range, "unexpected results [within the claimed narrow range] may... render the claims unobvious***" (see M.P.E.P. §2131.03). In the present case, while the '562 patent discloses a dose range which "touches" the claimed dose range of 0.01-0.1 mg/kg, the unexpected results provided by Applicants further prove that the pending claims are unobvious over the teachings of the '562 patent.

Den Broeder *et al.* fails to make up for the deficiencies of the '562 patent and the claims of the '015 patent. As discussed above with respect to the rejection under 35 U.S.C. 103(a), Den Broeder *et al.* report on a clinical study in which patients were subjected to a step-wise reduction in dose of D2E7 for treating rheumatoid arthritis at regular dosing intervals (every 2 or 4 weeks), *e.g.*, from 3.0 to 1.0, 0.5 and eventually to 0.25 mg/kg. Den Broeder *et al.* report that "six out of 21 patients were placed back on the original dose of 3.0 mg/kg after flaring on 1.0 mg/kg, whereas nine, three and three patients respectively reached a dose of 1.0, 0.5 and 0.25 mg/kg." Based on these results, Den Broeder *et al.* disclose that "the ***median of the calculated weekly dose*** of anti-TNFα administered to these patients was ... 32.5 mg week" (page 641, second paragraph), which is equivalent to ***0.36 mg/kg*** per week for a 90 kg person. Thus, den Broeder *et al.* fail to teach or suggest a method of treating arthritis by administering a dose lower than 0.25 mg/kg, let alone a low dose of ***0.01-0.1 mg/kg***, of a TNFα antibody, as required by the instant claims. Moreover, one of skill in the art would not have been motivated to arrive at the claimed invention, *i.e.*, to select the claimed dosage range of 0.01 to 0.1 mg/kg, based on the disclosure of den Broeder *et al.*, since den Broeder *et al.* teach that ***only three out of 21 patients reached the dose of 0.25 mg/kg***, while ***18 patients experienced a flair in disease at even higher doses***. Thus, den Broeder *et al.* ***teaches away*** from the claimed low dose of 0.01-0.1 mg/kg. Accordingly, one of skill in the art would not have had the motivation

nor a reasonable expectation of success in arriving at the claimed invention based on the teachings of den Broeder *et al.*

In view of the foregoing, it is evident that the claims of the '015 patent in view of the teachings of the '562 patent and den Broeder *et al.*, alone and/or in combination, fail to render the claimed invention obvious. Accordingly, Applicants respectfully request that the rejection of claims 1-4, 8-11, 15-17, 21-24, 28, 29, 31-36, 40-45 and 48-51 under the judicially created doctrine of obviousness-type double patenting be reconsidered and withdrawn.

Provisional Rejection of Claims 1-4, 8-11, 15-17, 21-24, 28, 29, 31-36, 40-45 and 48-51 Under the Doctrine of Obviousness-Type Double Patenting

The Examiner has provisionally rejected claims 1-4, 8-11, 15-17, 21-24, 28, 29, 31-36, 40-45 and 48-51 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 15-19 of co-pending U.S. Application No. 11/233,252 (hereinafter referred to as "the '252 application") and over claims 141, 142 and 159-166 of co-pending U.S. Application No. 09/801,185 (hereinafter referred to as "the '185 application"), both in view of the '562 patent and den Broeder *et al.* The Examiner is of the opinion that "[a]lthough the conflicting claims are not identical, they are not patentably distinct from each other."

Applicants respectfully acknowledge the provisional rejection of these claims. However, since neither claims 15-19 of the '252 application nor claims 141, 142 and 159-166 of the '185 application are presently patented or indicated as allowed, Applicants will address this rejection in the co-pending applications.

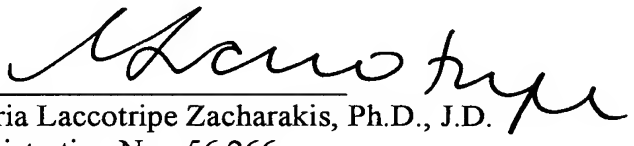
CONCLUSION

Reconsideration and allowance of all the pending claims is respectfully requested. If a telephone conversation with Applicants' Attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

In addition, Applicants include herewith authorization to charge fees associated with new claims and the extension of time with which to respond, to Deposit Account No. 12-0080, under Order No. BBI-190RCE. The Director is also hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to Deposit Account No. 12-0080, under Order No. BBI-190RCE.

Dated: **May 7, 2007**

Respectfully submitted,



Maria Laccotripe Zacharakis, Ph.D., J.D.
Registration No.: 56,266
Attorney for Applicants
LAHIVE & COCKFIELD, LLP
One Post Office Square
Boston, MA 02109
Tel. (617) 227-7400